Clinical Infectious Diseases

BRIEF REPORT

Multi-inflammatory Syndrome in Children Related to Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) in Spain

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Some clusters of children with a multisystem inflammatory syndrome (MIS-C) associated with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been reported. We describe the epidemiological and clinical features of children with MIS-C in Spain. MIS-C is a potentially severe condition that presents in children with recent SARS-CoV-2 infection.

Keywords. multisystem inflammatory syndrome; pediatric inflammatory multisystemic syndrome; COVID-19; SARS-CoV-2; Kawasaki disease.

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In the last weeks, some clusters of children with a multisystem inflammatory syndrome (MIS-C) linked to severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection have been described in the United Kingdom, France, Italy, and the United States, among other countries [1, 2]. This syndrome shares features of Kawasaki disease, toxic shock syndrome, and macrophage activation syndrome [3]. Some of these children tested positive for SARS-CoV-2 real-time reverse-transcriptase polymerase chain reaction (RT-PCR) and/or had a positive serological response for this infection. The specific link with SARS-CoV-2 remains unclear. In Spain, this phenomenon has also been observed.

OBJECTIVE

In this case series, we intended to describe the epidemiological and clinical features of children with MIS-C in Spain.

METHODS

This is a case series of children with MIS-C associated with SARS-CoV-2 enrolled in the Epidemiological Study of COVID-19 in Children of the Spanish Society of Pediatrics (EPICO-AEP), from 1 March to 1 June 2020. EPICO-AEP is a multicenter national study aiming to describe the coronavirus disease 2019 (COVID-19) in Spanish children. Children <18 years with infection due to SARS-CoV-2 and attended at 49 hospitals were included in this registry. Inclusion criteria included positivity in real-time RT-PCR positive, immunoglobulin M (IgM) or immunoglobulin G (IgG) in lateral-flow rapid test, enzyme-linked immunosorbent assay (ELISA) or immunochemiluminescence serology (see Table 1), or severe disease suggestive of MIS-C and recent household contact with a confirmed patient with COVID-19.

RESULTS

By 1 June, 312 patients had been attended in the 49 hospitals, and 252 participants were hospitalized. Of them, 181 (72%) were admitted due to causes directly or likely related to SARS-CoV-2. The remaining 71 (28%) were admitted due to causes not related with SARS-CoV-2 but were screened and found to be infected with SARS-CoV-2. A total of 31/252 (12%) children were diagnosed as MIS-C and/or Kawasaki disease by their physicians.

Weekly admissions of children with MIS-C and children with other clinical presentations associated with COVID-19 were recorded (Figure 1). The peak of MIS-C cases was 1 month after the peak of admissions for other COVID-19 related reasons and decreased afterward.

Table 1. Clinical, Microbiological, and Laboratory Features of Children With Multisystemic Inflammatory Syndrome Associated With SARS-CoV-2 in Spain

Categorical Features		Observed Cases / Patients
Demographic		
Male		18/31 (58%)
Comorbidities		
Asthma		4/31 (13%)
Obesity		3/31 (10%)
Chronic cardiac disease		1/31 (3%)
Chronic hematologic disease		1/31 (3%)
Neoplasm		1/31 (3%)
SARS-CoV-2 evidence		
Reverse-transcriptase PCR positive		17/31 (55%)
IgM for SARS-CoV-2 positive[a,b]		10/17 (59%)
IgG for SARS-CoV-2 positive[b]		19/21 (91%)
Reverse-transcriptase PCR positive and IgG for SARS-CoV-2 positive		7/21 (33%)
Any microbiological test positive		30/31 (97%)
Close contact with a COVID-19 patient		16/31 (52%)
Codetections		6/21 (29%)
SARS-CoV-2 and metapneumovirus		2/21 (10%)
SARS-CoV-2 and IgM positive for *M. pneumoniae*		1/21 (5%)
Clinical features		
Fever ≥3 days		30/31 (97%)
Rash or bilateral conjunctivitis		23/31 (74%)
Hypotension or shock		15/31 (48%)
Gastrointestinal problems (abdominal pain, vomits, diarrhea)		27/31 (87%)
Fatigue / malaise		15/29 (51%)
Cough		11/31 (36%)
Shortness of breath		8/30 (27%)
Sore throat		8/31 (26%)
Myalgia		5/28 (18%)
Headache		6/29 (21%)
Altered consciousness / confusion		4/31 (13%)
Lymphadenopathy		4/31 (13%)
Outcome		
Died		1/31 (3%)
Cardiological complications		19/31 (61%)
Myocardial dysfunction		15/31 (48%)
Pericardial effusion		6/31 (19%)
Valvular dysfunction		9/31 (29%)
Arrhythmias		7/31 (23%)
Coronary abnormalities		3/31 (10%)
Continuous features	**Observations**	**Median [IQR]**
Age (years)	31/31 (100%)	7.6 [4.5;11.5]
Total days of fever	30/31 (97%)	6.00 [5.00; 8.00]
Days of fever at admission	30/31 (97%)	5 [3.00; 6.00]
Heart rate at admission for (beats per minute)	30/31 (97%)	127 [118; 148]
Respiratory rate at admission (breaths per minute)	18/31 (58%)	30.0 [27.0; 34.8]
Oxygen saturation at admission (room air)	29/31 (93%)	98.0 [96.0; 99.0]
C-reactive protein (mg/L), worst value	31/31 (100%)	166 [83.7; 233]
Procalcitonin (ng/mL), worst value	29/31 (94%)	6.74 [1.65; 10.8]
D-Dimer (ng / mL), worst value	30/31 (97%)	2896 [2059; 5355]
IL-6 (pg / mL), worst value	23/31 (74%)	133 [41.3; 324]
Ferritin (ng/mL), worst value	29/31 (94%)	627 [365; 1278]
NT-proBNP (pg/mL), worst value	22/31 (71%)	8918 [4136; 14 255]
Hemoglobin (g/dL), worst value	31/31 (100%)	10.3 [9.00; 11.2]
Leukocytes (cells/mm3), worst value	31/31 (100%)	9560 [7365; 17 850]
Neutrophils (cells/mm3), worst value	30/31 (97%)	6810 [5725; 14 355]
Lymphocytes (cells/mm3), worst value	31/31 (100%)	910 [500; 1700]

Abbreviations: COVID-19, coronavirus disease 2019; IgG, immunoglobulin G; IgM, immunoglobulin M; IL-6, interleukin 6; IQR, interquartile range; PCR, polymerase chain reaction; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

[a]All patients with IgM positive had also IgG positive.

[b]Test used and performance according manufacturers: Immunochemoluminescence Abbot™ SARS-CoV-2, (S = 96% at 14 days, Sp = 99.6%), n = 15; Euroimmun™ (Sensitivity [S] = 94%, Specificity [Sp] = 100%), n = 4; Immunochemoluminescence Diasorin™ SARS-CoV-2 S1/S2 IgG, S = 97%, E = 98%, n = 1; ELISA in-house total antibody test, included within Solidarity II trial, ongoing and results pending, n = 6; Rapid Test BioZek™, IgM (S = 85%, Sp = 96%), IgG (S = 99.9%, Sp = 88%), n = 3; Immunoassays Elecsys SARS-CoV-2 Cobas™, total antibodies, S = 84%, Sp = 100%, n = 2.

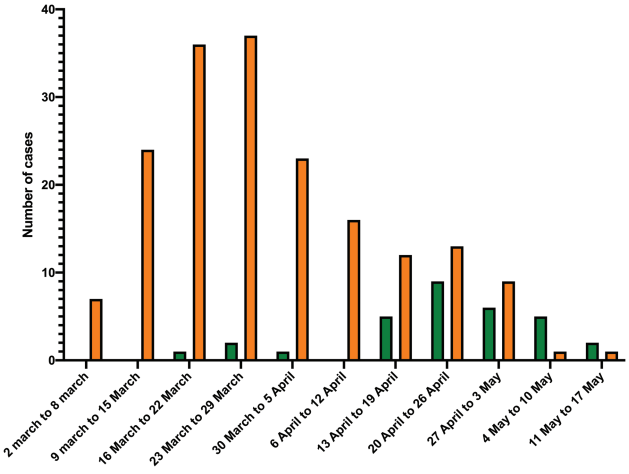

Figure 1. Weekly number of admissions of children due to multisystem inflammatory syndrome associated with SARS-CoV-2 (dark) and due to other presentations of COVID-19 (light). Abbreviations: COVID-19, coronavirus disease 2019; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

Median age and interquartile range were 7.6 (4.5, 11.5) years. A total of 30 (97%) children had microbiological or serological evidence of SARS-CoV-2 infection, and the remaining patient, an 11-year old boy with incomplete Kawasaki disease and pericardial effusion, had epidemiological household contact with a COVID-19 adult patient (his father, who is a health worker). Seventeen children (17/31; 55%) had positive SARS-CoV-2 RT-PCR in any of up to 2 respiratory samples (nasopharyngeal/oropharyngeal swab or bronchial aspirate); IgM was positive in 10/17 (59%) and IgG in 19/21 (90%). All patients with IgM positive also had IgG positive. Seven out of 21 (33%) patients had both RT-PCR and IgG positive, and 16/29 (52%) had a household contact with a confirmed COVID-19 patient (see Supplementary Table S1 for details on microbiological and serological results).

The World Health Organization (WHO) recently released diagnostic criteria for this condition [4]. All the described patients fulfilled the WHO case definition for MIS-C, except for 1/31 patients (3%).

Rash or bilateral nonpurulent conjunctivitis, or mucocutaneous inflammation signs were found in 21/31 (67%) patients; hypotension or shock in 15/31 (48%), features of myocardial dysfunction 25/31 (80%) consisting of pericarditis, valvulitis, arrhythmias or coronary abnormalities in 19/31 (61%); 6 (19%) additional children had only an elevation of a biochemical marker of heart dysfunction (NT-proBNP); evidence of coagulopathy (specifically, elevated D-dimers) was found in 29/30 (97%), and acute gastrointestinal problems (diarrhea, vomiting, or abdominal pain), in 27/31 (87%). No other apparent microbial cause of inflammation as sepsis or staphylococcal or streptococcal shock syndrome was found.

The patient who does not include WHO criteria was a 12-month old girl. The criterion she did not meet was the elevation of inflammatory markers. She was cohousing with a COVID-19 patient. She was on chronic oral treatment with steroids due to a chronic idiopathic interstitial lung disease. She presented with 6 days of fever, shortness of breath, and cardiogenic shock (pH = 7.2). She had lymphopenia (1100 cells/mm^3). She was diagnosed with cardiogenic shock. Echocardiography showed left ventricle dilatation above +2.6 Z-score for age and sex, and ejection fraction of 55%. Enterovirus infection was ruled out with PCR in nasopharyngeal aspirate. She received 10 days of remdesivir. Although she had low inflammatory markers, this fact was attributed to the long-term immunosuppressive therapy with steroids. She had a coinfection with human metapneumovirus (hMPV). She was treated for MIS-C with intravenous immunoglobulin (IVIG) and steroids. She was on long-term oral steroids due to pulmonary interstitial disease, which may avoid the rising of acute-phase reactants.

Thirteen children (45%) fulfilled the criteria of complete or incomplete Kawasaki disease. Other clinical features and laboratory values are summarized in Table 1.

Twenty (65%) patients needed admission to the pediatric intensive care unit, and 6/31 (19%) invasive mechanical ventilation. Cardiac complications consisted of myocardial dysfunction (15/31; 48%), pericardial effusion (6/31; 19%); valvular dysfunction (9/31; 29%), arrhythmias (7/31; 23%), and coronary abnormalities (3/31; 10%, among them 1 aneurysm). Four patients (13%) had renal failure.

Two (6%) patients received remdesivir and 7/31 (23%) lopinavir/ritonavir. A total of 21/31 (68%) children received corticosteroids: 19 of them received methylprednisolone (13 patients received doses of 1 to 2.5 mg/kg/day; 2 patients received boluses of 8 and 30 mg/kg/day for 3 days; 4 had dosing not available), 20/31 (65%) patients received 2 gr/kg of IVIG, and 13/31 (42%) patients received both IVIG and corticosteroids. All but 3 patients received broad-spectrum antibiotics.

One patient with acute leukemia and bone marrow transplant died, and one 6-month-old patient developed anterior-descendant coronary aneurysm (Z-score +9). This patient was an infant with Down syndrome, who presented with 5 days of fever, shortness of breath, and shock due to myocardial dysfunction. He had a positive RT-PCR for SARS-CoV-2 at diagnosis and coinfection with hMPV, proBNP = 9968 pg/mL, and troponin I = 34.1 ngr/mL. He developed valve insufficiency, renal failure, coronary aneurysm, and eventually had 50 days of fever despite treatment for infection (antiviral treatment with 2 days with lopinavir/ritonavir, hydroxychoroquine, cefotaxime, vancomycin, meropenem and micafungine), and for Kawasaki disease (IGIV and steroids). The rest of the patients recovered without sequels.

DISCUSSION

In this registry, entry criteria was COVID-19 disease, which is different from the previous reports that include patient without SARS-CoV-2 [1, 3]. Previous reports raised discussion as some children with MIS-C or Kawasaki disease lacked evidence of infection with SARS-CoV-2. Disease triggered by other causes may have been included within those reports. Our data strongly support the idea that not only is there a temporal association with SARS-CoV-2 but also a microbiological association.

In this report, only 1 patient without microbiological or serological evidence of SARS-CoV-2 was included, but he had a strong epidemiological link. There is a possibility that not all MIS-C cases are microbiologically related to SARS-CoV-2, because RT-PCR and serology do not have 100% sensitivity and specificity. That is why we have included a patient with negative tests and with recent contact with a patient with COVID-19, according to WHO definition of MIS-C.

Some children included may present other viral infection matching criteria of MIS-C and a positive test for SARS-CoV-2 reflecting only past or asymptomatic infection. Also, some children with acute COVID-19 might fulfill WHO criteria. On the other hand, children with Kawasaki disease may fit the WHO case definition and could have positive tests for SARS-CoV-2 simply because the virus is so widely circulating. This may happen with the 6-months infant reported, but given the cardiogenic shock, the proBNP figures, and additional features, we considered the disease as MIS-C. With all their limitations, only consensus criteria are currently available. According them, our data point to a microbiological relationship between SARS-CoV-2 and MIS-C.

Limitations of this study include that some cases without microbiological, serological or epidemiological link may not have been included in this registry.

SARS-CoV-2 could be a relevant trigger for a delayed cytokine storm and an inflammatory condition, with potentially severe consequences [5]. Coinfections such as hMPV may be present and might play a role in triggering the immune response. It is possible that some particular patients with special features—as chronic immunosuppressive treatment influencing inflammatory markers—may have MIS-C but not fulfill all WHO criteria.

CONCLUSIONS

MIS-C is a potentially severe condition that presents in some children after SARS-CoV-2 infection. Until herd immunity or a vaccine are available, physicians should be aware of this severe condition in children during COVID-19 epidemics. More studies are necessary to clarify the physiopathology of this syndrome and its adequate treatment.

Supplementary Data

Supplementary materials are available at *Clinical Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

Author contributions. A. T. and C. M. conceptualized and designed the study. M. S. performed data management and statistical analysis. C. M. and A. T. drafted the manuscript. All coauthors enrolled participants and participated in the collection of data. All coauthors participated and were involved in the critical review of the final manuscript.

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